MEDICAL RECORD

AN INTERNATIONAL JOURNAL OF MEDICINE AND SURGERY

Founded 1843

Vol. 163, No. 6 | JUNE, 1950 | Whole No. 2808

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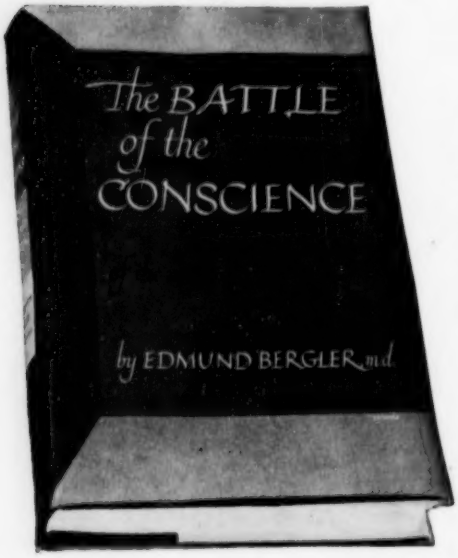

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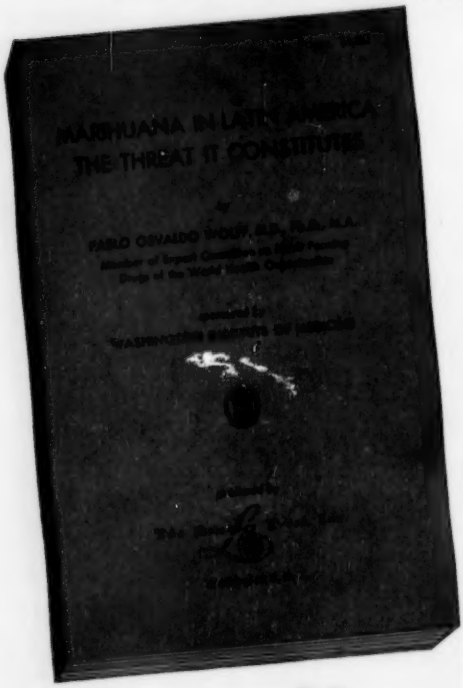
An important book for every physician... vital data on Marihuana Addiction



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The Enigma of Arteriosclersis

A Short Summary of the Literature

Aaron Stolinsky, M.D.

"Arteriosclerosis" is a term loosely used by clinicians to connote changes in the arteries which are characterized by hyperplasia, fibrosis, and degeneration of their walls, and are distinguished in the living subject by a variety of signs and symptoms, due to disturbances in function in the organs or other structures supplied by these arteries.

The most common arterial lesion is arteriosclerosis[1]; although this is chiefly a senile condition, it frequently begins in youth. It is of two chief types: 1) the *atherosclerosis* of the largest aortic branches, coronary, visceral, and cerebral vessels, which resembles that found in the aorta and 2) the *medial sclerosis*, also called *Mönckeberg's sclerosis*, found in the blood vessels of the extremities.

For several years it has been recognized[2] that cholesterol is present in the atheromatous plaques of arteriosclerosis. There has been no agreement as to the mechanism of entry of cholesterol into the intima of the arteries. The two most recent theories as to the mechanisms are those of Hueper and Leary. Hueper has suggested that the cholesterol enters into the subintimal tissues by simple inhibitions as a result of a disturbance of the plasmotic colloidal equilibrium which holds it in solution. According to this theory, the cholesterol appears first as an extracellular material which, as an irritant, produces fibrosis. The cholesterol is later taken up by phagocytic cells to form the so-called lipophages.

Leary has suggested, on the other hand, and has marshalled considerable evidence from experimental animals in support of his theory, that the cholesterol is esterified in the parenchymal cells of the liver. He postulated that under conditions of being overloaded the hepatic cells become unable to metabolize the material, presumably are damaged, and are phagocytosed by the Kupfer cells. The Kupfer cells, now lipophages, enter the blood sinuses of the liver, are carried through the lungs, and finally enter the systemic circulation.

It can only be concluded at this time that the pathogenesis of atherosclerosis is not yet understood.

Many attempts have been made[3] to prove or disprove the existence of relations between the cholesterol content of the blood and the development of atherosclerosis by comparing the cholesterol content of the blood with the conditions of the arteries. The results obtained were contradictory, as might be expected from the fact that atherosclerosis is in general a process

which takes years to develop and which may persist for many more years after the cessation of the action of the causal agent. The determination of the blood cholesterol content, on the other hand, merely renders information about the momentary condition of the blood, which may be entirely unrelated to the status of the blood prevailing when the vascular lesions were produced. Liebig found hypocholesteremia in 77% of his patients with atherosclerosis and essential hypertension and concluded from this observation that cholesterol contributed to the development of the vascular lesions.

Cholesterol present in the blood and in the tissue is in part synthesized in the body[4]; in part it originates from the original food ingested, especially eggs, butter, milk, lard and meat. Phytosterols contained in vegetable matter are not absorbed by the animal organism. Bloor stated that milk contains about 0.2 Gm. of cholesterol per liter, egg yolk about 1.9 Gm., and skeletal muscle 0.07 to 0.09 Gm. per kilogram. Hueck estimated that a baby when breast-fed consumes daily about 49 to 97 mg. of cholesterol, and when on a mixed diet about 62 mg. He estimated that adults on a fat-poor diet receive between 39 and 109 mg. daily, those on a mixed diet between 200 and 362 mg., and those on a high fat diet up to 1,400 mg. Round beef contains cholesterol 0.4% and sardines 0.19%. Milk contains cholesterol mainly in the form of esters whereas meat and brain contain mostly free cholesterol.

Cholesterol added in a dry form of food poor in fat is not absorbed by the intestinal mucosa. Foodstuffs rich in fat and oil, on the other hand, dissolve cholesterol, which is emulsified in the intestine through the action of bile acids particularly by desoxycholic acid and its alkaline salts, less by taurocholic and glychocholic acid. In the absence of fatty acid, free and esterified cholesterol does not pass the intestinal mucosa. The lymph of the thoracic duct contains 25 to 30% of the total cholesterol in the free form; the balance is in the ester form bound to fatty acids. A similar ratio (2:1) of esterified cholesterol to free cholesterol is noted in the plasma, which normally contains from 130 to 230 mg. of cholesterol in 100 cc., while the bile contains from 39 to 61% free cholesterol. Cholesterol is not readily degraded metabolically and is excreted with bile, sebum, milk, intestinal secretion, urine, through the skin and the lungs. The plasmatic cholesterol represents the bulk of the total blood cholesterol content as only relatively minor amounts of cholesterol are contained in leukocytes and erythrocytes.

Lake, Pratt and Wright[5] have undertaken a study of a small group of patients with the primary objective of developing data which might throw further light on our understanding of the production of arteriosclerosis from an occupational point of view. They came to the following interesting conclusions:

1. Men had a higher incidence of arterial disease than did women of the same ages who had been employed at similar occupations an equal length of time. Among the younger men (age 40 to 49) stair-climbing apparently produced a significantly higher incidence of arteriosclerosis than did standing,

sitting or walking. No significant difference could be established among the last three classifications. Over the age of 50 there were no significant differences in the incidence of arterial disease in any of these classifications.

2. The use of alcohol and tobacco did not influence the incidence of arteriosclerosis in the series studied.

3. There was a higher incidence of arteriosclerosis of the leg arteries in men with varicose veins. This difference was not satisfactorily established in women.

4. There was a definite relation in both sexes between the incidence of hypertension and of arteriosclerosis of the extremities.

Vartiainen, Illman, Konerva and Kari compared the incidence of arteriosclerosis found at autopsies during the war years with that in peacetime. During the recent war Finland had shortages of meat, eggs, milk, butter, and grain products. Caloric deficiency was compensated to some extent by vegetables, chiefly potatoes and rutabagas, but weight loss was common. Because this diet was low in cholesterol intake and high cholesterol intake has been incriminated as the cause of arteriosclerosis, the present study was undertaken.

Autopsy records were scrutinized for evidence of arteriosclerosis of the endocardium, ascending aorta, abdominal aorta, coronary arteries, thoracic aorta, and brain arteries. Records of autopsies performed in 1940–46 were contrasted with those done in 1933–38. Incidence of arteriosclerosis during war differed little from that during peace in patients under 30 and over 70. However, arteriosclerosis was more than twice as common during peace time in patients 30–39; similarly but slightly smaller differences were found in patients 40–69. In vital statistics of Finland, arteriosclerosis was about twice as common as a cause of death in peace years as in war years.

The authors suggest that arteriosclerosis is not a process of degeneration inevitably connected with old age but the result of certain aspects of diet and is therefore preventable. The particular aspects of diet associated with arteriosclerosis are unknown. High cholesterol diet may be the cause of arteriosclerosis. High protein diets are known to elevate the blood level of cholesterol. The mechanism by which obesity shortens life remains unknown.

Kodachrome photographic slides of the intimal surfaces of aortas and main branches of the coronary arteries of 104 patients aged 40–60 were prepared by Sigmund L. Wilens.[7] These slides were arranged as unknowns in the order of severity of their intimal plaques, and severity of arteriosclerosis was then correlated with 1) the patient's weight during life and 2) terminal weight loss. Almost half the patients had lost large amounts of weight during the year preceding death.

Severe coronary atherosclerosis was found in 12 (50%) of 24 obese but only in 2 (5%) of 39 poorly nourished patients. Severe atherosclerosis of the aorta was found in 10 (42%) of 24 obese but in only 6 (15%) of 41

poorly nourished patients. Severe coronary atherosclerosis was present in 18 (28%) of 65 patients who had not lost weight and in 8 (20%) of 39 who had lost weight.

The authors infer that weight loss is associated with regression of atherosclerosis. Microscopic study indicated that regression of atherosclerosis was associated with diminution in size and number of fat-containing phagocytes in atheromatous lesions.

The evidence that obesity and hypercholesterolemia predisposed to coronary sclerosis seems overwhelming. The evidence that in the absence of hypercholesterolemia the amount of cholesterol in the diet is important is becoming stronger. The evidence that atheromatous deposits may be reabsorbed is suggestive, but not entirely convincing. In prescribing low caloric diet it should be remembered that rapid weight reduction causes the patient to utilize large amounts of his own fat, and hence is equivalent to a high fat diet. Hence weight reduction should usually be carried out slowly rather than rapidly. The present evidence, while not conclusive, suggests that diets which are very low in animal fat and moderately low in total calories are optimal for prevention and probably for treatment of arteriosclerosis.

As has already been mentioned there are a number of observations that indicate that the general nutritional state of a person may have an important bearing on the formation of the atherosclerotic lesions. These observations[9] may be divided into two categories: 1) those suggesting that obesity favors rapid and extensive development of atheromatous plaques and 2) those indicating that prolonged under-nutrition may retard the formation of such lesions.

Chief among the first group are the extensive statistics of insurance companies in which it is shown that important clinical consequences of atherosclerosis (e. g., occlusion of the coronary artery and cerebral hemorrhage) occur more commonly in obese persons than in persons of average nutrition or in the undernourished. The most plausible explanation of this finding is that the atherosclerotic process is more advanced in the obese group. The alternative explanation is that the lesions themselves may not be more severe in obese than in other persons but that the extra mechanical burden imposed on the cardiovascular system by excessive deposits of fat tissue may lead to greater impairment of function.

Diabetes mellitus and arterial hypertension are two conditions that are widely held to predispose to the development of atherosclerosis. There is considerable evidence that both occur more commonly in persons who are overweight than in those who are underweight.[10] In Cushing's syndrome, in which obesity is coexistent with both diabetes and arterial hypertension, a tendency for severe atherosclerosis to develop has been noted. The part that obesity itself may play in producing the arterial lesions in these disorders has not been clearly elucidated. Joslin[11] attributed the severe atherosclerosis of diabetic patients to the associated obesity. Severe atherosclerosis was reported by Kuczynski to occur at an early age among

nomads of the Kirghiz Steppes. A high incidence of obesity occurs in this population, due to the consumption of unusually large amounts of food. French and Dock reported that of 80 young soldiers dying of coronary arteriosclerosis, 73 were overweight. Finally, the incidence of obesity increases progressively with age in much the same fashion as the incidence of atherosclerosis.

In parts of the world where poor nutrition is prevalent, a low incidence of atherosclerosis has been reported. This appears to be particularly true of China and some of the Central American countries. In China, Oppenheim,[12] and more recently, Snapper observed little atherosclerosis even in persons dying at an advanced age. In China, Oppenheim noted that even in the presence of syphilitic aortitis there were no superimposed atherosclerotic plaques in the aortic intima. In the United States and Europe syphilitic aortitis and atherosclerosis are often coexistent.

The low incidence of atherosclerosis in China is sometimes attributed to dietary factors or to related arterial hypertension. It is true that neither arterial hypertension nor diabetes is common in that country, but the degree of atherosclerosis noted at necropsy is apparently even milder than that observed as a rule in nonhypertensive and nondiabetic persons in the United States. The difference of mean systolic blood pressure in China and the United States is less than 10 mm. of mercury. Therefore, it seems doubtful that this slight difference could account for the variations in severity of arteriosclerosis.

Weiss and Minot stated that there is no evidence that patients with chronic pulmonary tuberculosis may enjoy relative freedom from atherosclerosis. In such patients severe malnutrition is commonly present. In the examination of arteries of tuberculous patients at necropsies in the department of pathology at New York University little atherosclerosis has been found, particularly when severe undernutrition was present.

Coronary sclerosis, according to Plotz,[13] is somewhat different from arteriosclerosis of the vessels of the extremities which one commonly thinks of in connection with the term "hardening of the arteries." In the extremities it is a lesion involving mostly the media with very little thickening of the intima, especially in the early stages. On the contrary, coronary sclerosis starts as a thickening of the intimal layer, and throughout its course, even in its most advanced stages, nearly all of the disease is localized in the intima with involvement of the media as a late and comparatively unimportant process. The pathologic process then is an atheroma, and the disease is best referred to as atheromatous rather than arteriosclerosis. One other point deserves attention: coronary atheromatosis is the only important disease of the coronary arteries; other lesions comprise less than 10% of all cases and are clinical curiosities. In other words, if the patient has any disease involving the coronary arteries—angina pectoris, coronary thrombosis or myocardial infarction—one can be reasonably certain that one or more of his coronary arteries has atheroma.

Moreton[14] advanced an hypothesis which may be of great importance. He presented evidence that high fat meals induce hyperlipemia, that the size of the lipid particles is comparable to that of particles known to produce arteriosclerosis experimentally, that the intima may take up these particles and "foam cells" may be found and that the triglycerides and fatty acids are more readily absorbed and removed than cholesterol, which remains as the "difficult-to-remove residue." "When this residue of inert and difficult-to-resorb cholesterol is thus trapped between the high-pressure blood column on one side and the internal elastic membrane on the other, it is withheld and prevented from being dispatched to the liver (and possibly other sites), where theoretically it could be relatively easily degraded or eliminated by cells that are specialized in such metabolic functions. Thus, the accumulation of lipids in the arterial intima seems to be a local, mechanical problem, and unrelated to general body balance or over-all metabolism of these substances." He advanced the theory that the cumulative effect of many fatty meals is to produce transient showers of large lipid deposition in human atherosclerosis. Theoretically, too, even if there is no cholesterol in the meal, the lipid particles may carry with them cholesterol already in the blood stream, or cholesterol released in the bile used to digest these fats.

In any case, whether one accepts the "cholesterol theory" of the induction of atheroma or not, the evidence to date is such that one should proceed with caution in the prescription of high fat diets to patients with known coronary disease.

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Carcinoma and Arteriosclerosis

Factors Concerned in the Altered Calcium-Binding Mechanisms in Cancer and The Aging Phenomena

R. de Rohan Barondes, M.D.

Among the more important studies that should command greater attention in the biological problems of carcinoma, atherosclerosis, hypertension, etc., are those concerning the disturbed acid-base equilibria that alter materially the calcium binding and enzyme mechanisms thus leading to the development of pathological processes.[1, 2, 3, 7, 8, 9, 12]

In considering the title of this article, it must be understood that the material upon which it is based is not too fixed or determined. Increased interest is being directed to the study of the biochemical processes concerned in the aging phenomenon, and concomitant disorders such as atherosclerosis, neoplastic growths, alkalosis and acidosis, that are correlated with such processes. Though conclusions are not yet possible, the following observations are reported at this time as an incentive to further investigation.

In health, the acid-base balance of the blood remains remarkably constant at a *p*H about 7.4 although carbonic, phosphoric, sulfuric, hydrochloric, lactic and carbonic acids are continually being formed in the processes of metabolism. The adjusting mechanisms called into play to neutralize and remove excess acid are extraordinarily efficient. Carbonic acid, a product of tissue activity, is produced in greater quantities (800–900 Gm. per day) than any other acid in the body. In diabetes mellitus, such fixed acids as hydroxybutyric and aceto-acetic acids are produced in excessive amount, and the adjusting mechanisms are unable to neutralize and remove the excess acids which then accumulate in the system.[1]

As is known, the normal reaction of the blood is protected by several lines of defense, e. g., the buffer systems, the excretion of CO_2, the chloride shift, and the excretion of fixed acids. Carbonic acid, H_2CO_3, is buffered mainly by a base released from hemoglobin, and to some extent in the plasma through the protein and phosphate systems. When carbon dioxide enters the blood, the sodium bicarbonate of the plasma increases. As the blood passes from the arterial side to the venous, CO^2 is absorbed and diffuses into the red blood cells. In these cells through the action of an enxyme, carbonic-anhydrase, the CO^2 is converted into carbonic acid.[1]

A decreased production of carbonic acid (alkalemia) over a period of time causes a supersaturation of the blood with lipid-calcareous matter which, being insoluble in excess alkaline media, is thrown out of solution to be often deposited abnormally in the tissues. This with a disturbance in

phosphatase systems, appears to be a primary factor in the etiology of arteriosclerosis, Paget's disease, myositis ossificans, calcinosis universalis, and other similar metabolic disorders. During rest, the *p*H of the venous blood is reduced (7.28), being more acid than that of the arterial blood (7.4). The salts here are more readily maintained in solution, and this factor would explain the rarity of a phlebosclerosis.[4, 5, 9, 13]

In disordered blood states, e. g., in the case of dysfunction or inactivation of the enzyme, carbonic-anhydrase, carbon dioxide conversion is interfered with; the carbonic acid becomes decreased, while the bicarbonate is increased. This results in an alkalemia. When carbonic acid production is increased, the bicarbonate becomes reduced as the base is given up for the neutralization of the strong acids, and an acidemia results. Carbonic acid readily dissolves calcium carbonate to a considerable extent, forming a soluble acid-calcium carbonate.[1]

It is in accord with the laws of chemistry that the diffusibility of calcium, magnesium, and phosphorus varies with the *p*H of the media. For proper metabolism, not only must the ratio between these elements be maintained, and the absolute amount of each at the ratio, but the diet and the digestive and other body fluids in general must also remain in proper hydrogen-ion concentration. In a well-marked case of rickets, for example, the gastric juices not only are less acid than normal but calcium retention is low, the intestinal contents becoming decidedly alkaline. This cannot be conducive to the absorption and utilization of calcium, magnesium and phosphorus. Vitamin D here, in addition to other effects, is of benefit as it also lowers the *p*H of the intestinal secretions thereby facilitating proper absorption and utilization of these essential agents. Plasma is normally poor in magnesium and potassium but rich in calcium and sodium; whereas in the cells the conditions are reversed, these showing a high concentration of magnesium and potassium and low in calcium and sodium.[1] A magnesium deficiency, clinically, is indistinguishable from a calcium deficiency. When animals are kept on feedings too high in magnesium carbonate, there results a high incidence of renal calculi and other disorders, a state that may also apply to man. These disorders can be corrected and prevented by the addition of excess calcium carbonate to the diets. A magnesium deficiency, by causing a relative calcium excess in the body, is indirectly incriminated in the etiology of atherosclerosis, and certain other calcium metabolic disorders.[1, 3, 4, 12] However, this is of secondary concern at the moment. Magnesium has the positive function in the body of ion balance, enzyme activation, and the maintenance of the proper *p*H of the blood and tissues. It also plays an important role in the biochemic and physiologic processes of both animal and vegetable life, preserving the electrolyte concentration of the fluids, and maintaining the important osmotic pressure of both intracellular and extracellular fluids. There is some direct relationship between the functions of the parathyroid gland and the biochemistry of magnesium, for in dysfunctions of this gland the body magnesium becomes reduced.[1]

There is a definite ratio between sodium and potassium, on the one hand, and calcium, magnesium, and phosphorus, on the other hand, in the healthy body. Though their ions have much in common, a disproportion or additions beyond these ratios speed up elimination of the others. Deficiencies also arise through insufficiencies in the diet, and from faulty utilization, absorption and/or interference by other mineral supplements, catalysts, etc., which reduce their availability.

Regulation of the Acid–Base Balance

The *p*H of the blood in health varies but little. In disease, the *p*H, except in the terminal stages of uremia, diabetic coma, eclampsia, extreme starvation, etc., rarely approaches 7.0. The limits of the *p*H compatible with life are probably neither higher nor lower than 7.8 and 6.8.[1] A *p*H of 7.0 results in complete heart block. This is the ultimate cause of death in starvation, where the blood pressure falls below the critical level of 60 mm. of Hg.[13]

A rise in blood hydrogen-ion concentration (alkalemia) causes not only a vasoconstriction but also acts as a stimulus to the vasomotor center, thus contributing to a general rise in blood pressure. In healthy carnivora the alkali reserve parallels the blood pressure; and in advancing years, when the growth-processes have subsided, an alkalosis is normal. When alkalis are ingested over long periods of time, the rise of H-ion concentration results in vasoconstriction, an elevation in blood pressure, and causes the circulating hemoglobin to hold its gathered oxygen more firmly. Such a condition obtains also in those with abnormal alkali retention. Alkali poisoning readily occurs in those abnormally sensitive to alkali therapy.[1, 2, 3] The important changes in the blood in an alkalotoxicosis are: a definite uncompensated alkalemia, increased C/N ratio, hypercalcemia and other manifestations. A long-standing alkalosis leads also to severe nitrogen retention, anoxemia, calcium and lipid depositions, fibrosis, early senescence, and tissue breakdown through lowered tissue respiration.[2, 3, 4, 13] Alkali therapy also exerts a deleterious effect upon the C and the vitamin B-complex, as both are unstable except in acid media. Several of the symptoms observed in a chronic alkalotoxicosis probably are due to such vitamin destruction.

An alkalemia, by causing vasoconstriction, leads to reduced blood supply to the vasomotor center so that a general blood-pressure rise occurs. Such a state also would exert adverse effects upon such normal vasodilating substances as acetylcholine, histamine, etc., which are susceptible to alkalotic states, and become inactivated or destroyed in any but acid media. The electrogenic properties of acetylcholine, along with the tissue acidity and body CO_2, provide the activating forces of the respiratory center.

Upon the ratio $H_2CO_3/NaHCO_3$ the *p*H of the plasma depends.[1] Rapid adjustments of this ratio are brought about mainly through the exquisite

sensitivity of the respiratory center to changes in *p*H, and the chloride shift mechanism. The slightest reduction in plasma-bicarbonate through its decomposition by acid is met by increased pulmonary ventilation with the elimination of carbon dioxide by the lungs. Low arterial and alveolar CO_2 tensions are therefore associated with a low alkali reserve. On the other hand, when excess CO_2 is contained in the blood, a compensatory increase in bicarbonate (chloride shift) results; so high arterial and alveolar tensions are associated with a high alkali reserve.

When excess CO_2 is removed from the body, as by forced breathing, a movement of bicarbonate and chloride ions occurs in reverse direction. The hydrogen-ion concentration of the saliva is found to vary directly with the CO_2 content of the blood; when CO_2 tension in the blood is high, more CO_2 finds its way into the salivary secretions to lower the *p*H. Ingestion of sodium-bicarbonate, while reducing the acidity of the urine, increases the acidity of the saliva as a CO_2 tension results. In forced breathing the H-ion concentration of the saliva is raised as it lessens the amount of CO_2 in the saliva. Under certain conditions a reduction in the alkali reserve can occur with little or no change in the blood reaction.[1]

Acidosis and Alkalosis

Much confusion has arisen over the terms "acidosis" and "alkalosis." Acidosis cannot mean any real acidity of the blood, i. e., a blood *p*H below 7.0, for this is incompatible with life. Alkalosis carries the corresponding meaning of an increased alkali reserve. This may or may not be associated with a rise in the blood *p*H.[1] The terms suggested for these acid-base states are alkalemia and acidemia. The British Medical Council has recommended that the term acidemia be used for a state in which the *p*H is lowered; and that the term acidosis be restricted to indicate only a lowered reserve with unaltered *p*H. Alkalemia would indicate a blood state in which the *p*H was raised; alkalosis would be retained to indicate an increase in the reserve alkalinity.

An alkalemia may obtain through an uncompensated alkali excess: the $NaHCO_3$ is increased without a proportional rise in the H_2CO_3. This results from ingestion of large quantities of alkali, or from loss of HCl as in severe sea-sickness and other prolonged vomiting states. An uncompensated CO_2 deficit also produces an alkalemia. A disturbance of this nature occurs from forced breathing, hyperventilation, high altitudes, etc., the increased alkalinity here occurring within the red blood cells. This condition is not uncommon to the less-experienced aviators, and would explain some of the adverse effects experienced in altitude flying prior to acclimatization. Hyperventilation symptoms also obtain in neurocirculatory asthenia, acting through the resultant respiratory alkalemia, and in hysteria, severe encephalitis, etc.

When there is an uncompensated CO_2 excess, an acidemia results. The carbonic acid is increased but is not balanced by a proportional rise in the sodium bicarbonate. The *p*H is lowered. This is noted in obstruction

to breathing, and in depression of the respiratory center by morphine.[1] The *p*H of the blood is also lowered in an uncompensated alkali deficit, the bicarbonate being reduced without there being a parallel reduction in the body acids. This happens when large quantities of fixed acids are produced, e. g., in diabetes, the terminal stages of nephritis, etc.

Arteriosclerosis

Innumerable factors apparently enter into the etiology of arteriosclerosis that present many challenging problems. The wide variety of etiological factors elicited through perusal of literature attests the lack of fundamental knowledge of this condition. (As there is no clear-cut conception of the various subdivisions, the generic term, arteriosclerosis, is used here to include atherosclerosis, Mönckeberg's sclerosis, arteriolar and senile.) That calcification plays a prominent role is not to be denied, but the factors determining the lime and lipid depositions remain a mystery. One important phase overlooked in the study is the disordered *p*H of the blood and tissues prior to the deposition of the lipid and lime material in the walls of the arteries.[2, 4, 13]

It is thought by some investigators that the onset of degenerative change is secondary to deterioration of the elastic tissue of the intima and media which, by weakening the arterial wall, permits distention of the vessel. The stretching, it is presumed, interferes with the blood supply of the vascular wall, the intimal thickening being looked upon merely as a compensatory process. Others believe that arterial calcification is simply a particular type of dystrophic calcification, not specific in nature, but induced by a toxic agent.

Calcium deposition in the arterial walls is often a pronounced feature of metastatic calcification, this term implying a translocation of calcium from the skeleton to the soft tissues.[1] Such an organic disturbance has been observed in animals fed excessive amounts of parathyroid, fluorine salts, lipid and cholesterol-rich food, irradiated ergosterol, vitamin D, etc. Though lipid-calcium deposits may occur in any of the soft tissues, the arteries, kidneys and lungs are most prone to calcification.

Lime salts, cholesterolester and lipid depositions, hyaline thickening and fibrosis readily occur in any tissues where the cells become more alkaline in nature.[1, 2, 4, 9, 13] As calcareous matter is readily deposited in lipid material in alkali media, the first evidences in the tissues of arteriosclerosis would then be cholesterol and lipid depositions. One such form arises from a hypothyroid state accompanied by a sustained hypercholesterolemia.

The arteriosclerotic changes from lipid-calcareous deposits would make their appearance first in the minute ramifying vessels (vasa vasorum) which readily become obstructed, this in turn leading to anoxia and degenerative changes in the intima of the vessels. The salts deposited in the affected tissues have the same composition as the main mineral constituents of bone. Dried bone contains about 31% organic matter combined with

69% mineral matter. Of this about 39% is tricalcium phosphate, 1½% magnesium phosphate, and 7% calcium carbonate. Human bone frequently contains calcium fluoride to the extent of 2%, though the quantity of fluorine compared with the other constituents of bone is extremely small. It may well play the part of a catalyzer, acting as a sensitizer for the phosphates and enabling the phosphorus and calcium to combine with the tissues. The percentage of fluorine in calcified vessels should be determined. The action of this element resembles somewhat the specific effects of sunlight and vitamin D, both acting as catalysts to aid calcium deposition, and building bone from the calcium and phosphorus complexes.[1]

Diet and Prophylaxis

The proper dietary and prophylactic measures appearing indicated in arteriosclerosis, hypertension, and certain calcium-lipid metabolic disorders, are diets that tend to keep the patient on the "acid side." A subcaloric diet is always beneficial as it increases tissue acidity, lowers the blood *p*H and the blood pressure. Contraindicated would be long-continued strictly vegetable-fruit diets on account of the high alkalinity ash, and likewise milk, eggs and other foods that are rich in cholesterol, animal fats and oils. With the exception of kidney, liver and brain, there is no justification for eliminating meat and fish from the diet. If edemic and like states are complications, then sodium chloride should be reduced to the minimum, and appropriate ammonium or potassium therapy instituted in order to speed up elimination of any excess sodium ions in the system. Absence of sodium, over a period of time, often results in severe muscular spasms that are more annoying to the patient than the hypertensive effects. NaCl is necessary to maintain a fairly chemical and fluid balance. A total lack of sodium is incompatible with life. Prolonged sodium abstinence has been known to lead to adrenal damage, interference in the body detoxifying processes, and uremic symptoms. The minimal daily requirement of two or three grams of sodium chloride would be of little harm in any state. When more may be indicated, any excess sodium ion in the system can be quickly eliminated through use of ammonium chloride, potassium chloride, etc.

An induced acidemia, i. e., the shifting of the *p*H toward the acid side by acidifying agents as phosphoric, hydrochloric and lactic acids, ammonium citrate and chloride, and other acidogenic agents, should aid in preventing further depositions of calcium-lipid material. This measure would also exert certain hypotensive effects, and the *p*H shift would be expected to cause some dissolution of the pathological lime deposits in the tissues.

In prior publications, the author[2, 12] advocated diets of acid ash and low caloric value, including those of high carbohydrate and low fat as rice, barley, whole wheat, buttermilk, consomme, cocoa, cranberry, rhubarb, etc., as the rational method to satisfactorily maintain depression of the blood pressure through the resulting acidogenic and weight-reducing

effects.[2] This more-natural method of maintaining reduced blood pressure has now received support by others. Thyroxin, insulin, choline and methionine are decholesterolyzing agents, and could find a place in the therapy of atherosclerotic and other abnormal conditions, the result of hypercholesterol states. Exercise in moderation is not contraindicated, in fact desired, as it creates lactic and other organic acids that lower the body's alkaline reserve, and consequently the blood pressure. (A strictly sedentary life without exercise raises the alkali reserve through lowered production of the body acids.) If, however, extensive degenerative changes have occurred in the arterial walls, the mineral salts and lipid material having replaced the normal muscular and elastic tissues, then no dietary or therapeutic measures would be likely to restore structures so injured, and would then be of no avail.

Hypertension, per se, is not a disease but a symptom complex peculiar to several hypertensive-producing effects, e. g., cardiorenal vascular disorders, exogenous and endogenous toxicoses, pressor drugs, etc. As with the atherosclerotic states, there is more than one etiologic type of hypertension, and more than one precipitating factor. One type, for example, results from intrarenal vascular imbalance with protein and tissue disintegration that releases pressor cleavage products as angiotonin, methylguanidine, adrenalone, and tyramine (from break-down of tyrosine and phenylalanine), agmatine (from arginine), and renin (tyramine?).

In extracts of kidney, and in urine, there are found pressor-counterbalancing substances. The loss of these pressure-reducing substances through excretion, destruction or production insufficient compared with the relatively large amounts of pressor substances produced, results in deficiency states. Several of these antipressor agents appear to be enzymes; one being tyrosinase which inactivates tyramine and prevents tyrosine and its precursor, phenylalanine, from breaking down to tyramine. Tyrosinase therapy would only be effective if the hypertension should be the result of a tyraminosis.[6]

Tissue-Calcium in Senescence and Carcinoma

Lansing[3] correlates the changes in intracellular calcium with age and malignancy. He notes that body calcium increases with age, and that among the cells calcium is increased in some locations and decreased in others. He found that the change in intracellular calcium is an important factor in both aging and malignancy, and that senile calcium increase occurs in the cell periphery.

This increased calcium apparently decreases permeability of the cell membrane producing an accumulation of metabolic waste products within the cell, and which in turn produces the changes associated with senescence. His studies to determine the effect of experimental alteration of the calcium content of the cells on longevity showed that under carefully standardized environmental, nutritive, and genetic conditions, the organisms living in a low calcium medium will live longer than those in control animals. The

experimental removal of calcium from the cells by sodium citrate results in a marked increase in longevity.

Calcium increases with age in the cell cortex, and a decrease extends the period of life. It has been found that intermittent fasting in animals extended their life span. The explanation lies in the fact that fasting is not conducive to calcium retention through the lowering of the *p*H of the tissues.[2] Reports show that a reduction of caloric intake also reduces the incidence of mammary cancer in susceptible strains of mice, and also inhibits development of leukemia induced by methylcholanthrene but not if the food intake is composed mostly of fats. This could be due to the high lecithin content that has anticarcinogenic properties.

The study of acid-base balance in health and disease should explain, materially, such problems as the increase of calcium in aging; the atherosclerotic and allied states; and the decrease of intracellular calcium in malignancy.

Should the body tissues and fluids not remain in normal acid-base equilibria, cell activity becomes altered, and certain parts eventually undergo pathologic and carcinomatous change. The change may be a degenerative one as that in arteriosclerosis, or the cell-enzyme systems may become deranged to result in altered biochemical activity with cell deficiencies of essential agents. Such tissue changes reduce resistance to bacterial and viral invasion.[2, 4, 13] Two diseases intimately allied to acid-base disturbances, are pernicious anemia and beri beri. In both disorders the spinal cord degenerates, apparently as a result of changes in the acid-base balance produced mainly by an achlorhydria and vitamin B_1 deficiency or destruction.[1] An hypochlorhydria often follows a B-complex avitaminosis, and vice versa.

The Mycobacterium tuberculosis requires media under *p*H 7.4 for optimum growth, pure cultures being best obtained in slightly acid media. Unlike most organisms, the tubercle bacilli are not killed by a 15% sulfuric acid solution. Cultures of the bovine type are at first acid but become alkaline, while those of the human species never do so. Tuberculin is highly acid. In tuberculosis, and also in leprosy, the alkali reserve shows the average figures of the actual acid-base reactions to be diminished. This fact alone would indicate instituting some form of alkalotherapy to help shift the *p*H toward the alkaline side.[12] The usual dietetic and therapeutic measures in both diseases are curative in that they do induce an alkalemia, raise the blood pressure, and aid in fibrosis, calcium and lipid deposition, with the walling-off of foci of infection. Hypotension is a common feature here, and an acidosis is one of the main complications. Preliminary data show that an acidemic state precedes and favors these infections. An acidotic state sets up a vicious cycle by retarding the processes of organic combustion which, in turn, furthers the increased acidity of the body tissues and fluids. The acidemic and hypotensive states are further aggravated by the low caloric intake, acidifying diets, and the fever accompanying the exhausting illness.

Induced alkalemia and restoration of the blood pressure in both tuberculosis and leprosy, favor lime deposition and fibrosis, and such areas then would inhibit bacterial growth. Residence in high dry climate helps raise the tissue *p*H, increases the red blood cells, induces hyperventilation, elevates blood-pressure, all highly desirable in aiding recovery. Sunlight and sub-erythema doses of ultraviolet irradiation are destructive to the bacilli, and such measures also aid in calcium lipid and cholesterol depositions, with the desired fibrosis and calcification at the sites of infection.[13]

Diets found beneficial in both disorders (but obviously contraindicated in atherosclerosis and certain allied disorders), are liver, brain, kidney, milk, cream, egg yolk, butter, cod liver oil, animal fats (rich in cholesterol), etc., all favoring hypercalcemia and lime deposition, with a general rise in the *p*H of the tissues. Vegetable oils lack cholesterol, and thus would serve no useful purpose in increasing the body cholesterol. Thyroid gland extract is contraindicated for while it increases the metabolic rate, it lowers the blood cholesterol content. (Insulin also lowers the serum lipid and cholesterol values.) Parathyroid and fluorine compounds have therapeutic value in tuberculosis and leprosy as they induce a cholesterolinemia, thereby aiding lipid-lime depositions, fibrosis, etc. Parathyroid extract also reduces the body phosphorus thus causing a reciprocal calcium increase. This hormone, with low calcium intake, mobilizes lead from the bones (plumbism), and aids liberation and excretion of radium deposits. Extracts of adrenal cortex would be of benefit in aiding proper glycolysis, and in supportive treatment to combat the effect of the toxins on this detoxifying gland.

Biochemical Disturbances in Carcinoma

In cancer tissue there is a marked fault in the metabolism of glycogen with an excess production of lactic acid and a lack of glycogen: the result of disturbed glycogen, hexosephosphate and other enzyme systems.[1, 8, 9, 12] The lactic acid resulting from the fault in the glycogen-lactic acid cycle does not collect, as a rule, in carcinomatous tissues. Apparently it is neutralized as it is produced, causing the calcium, sodium and other alkaline agents in the tissues to form lactates, in an endeavor to augment the alkaline reserve in response to the localized tissue acidosis. Such a morbid state could not be conducive to absorption and retention of intracellular calcium, and would explain the defect in the calcium-binding complex, and the local calcium deficiency in and about the carcinomatous tissue. There is some evidence of increased conversion of methylglyoxal to lactic acid in neoplasm, the acid causing hydration and water-logging of the cancer and pre-cancer cells. Plasmoptysis of cancer cells occurs from increased permeability of the cell membrane of lowered cell-calcium content. Physiologically, calcium tightens the cell membranes, preventing diffusion of potassium from the cells into the surrounding medium. A deficiency of calcium here then would facilitate cell potassium uptake. Potassium

itself, is known to accelerate cell growth. Cancer cells are low in calcium, magnesium, sodium and free cholesterol, and high in potassium, phosphatide and fatty acids. The venous blood from carcinoma contains more lactic acid than any other venous blood. This lactic acid later is converted to glycogen in the liver. Body tissue lower in glycogen by nature may be potential cancer tissue.

Recoverable from urine of cancer subjects is an unidentified tryptophane derivative with the chemical formula $C_8H_5NO_2$, appearing to be related to indigo, indole, and indole-acetic acid, but its significance has not as yet been determined.[9] This benzpyrrole derivative and its abnormal enzyme acting as a reducing agent, may be responsible for the decolorization of the methylene blue in the urine of cancer patients when this dye is given internally.* Several tryptophane decomposition products, e. g., indole-butyric and indole-acid, have marked growth-stimulatory effect on both animal and vegetable matter. However, the mere stimulation of cell multiplication and growth, without causing any intracellular disturbances, does not, in itself, cause malignancy. Substances that accelerate growth in small amounts generally inhibit growth in large amounts.

Experiments with analogues of tryptophane, or synthetic substances with similar molecular configurations (competitive analogues) might show that certain tryptophane derivatives are carcinogenic, and their effect might be counteracted by use of inert analogues to alter the intracellular metabolism. Further effort should be directed toward depriving malignant tissue of other essentials for continued growth by using the competitive analogues of nutrient components utilized by the neoplasms.

As the nuclear material of the body tissue cell is sensitive to extrinsic carcinogenic effects, and is closely related to virus reproduction and growth, morbid degradation products of the cell nuclear protoplasm, of virus-like nature, could be the true carcinogens that stimulate growth by indirect cell division. The breakdown of cancer cells liberates numerous nuclear cleavage and protein degradation products that are more or less antigenic, and which upset the cell regulatory mechanisms of reproduction and growth. The body, to a certain degree, is capable of elaborating specific anti-enzymes to render these products innocuous. Among these agents suitable antigens may be found which would initiate body response with the formation of specific corresponding enzymes that would affect the deranged enzymes in carcinomatous tissue to render them inactive and aid in the restoration of the normal-acting ferments. These antigens might be ob-

*Methylene blue is decolorized to the reduced state by the reductases in malignant material, the color returning on the addition of oxidizing agents. When malignant tissue is treated with methylene blue and then with prontosil solution, a purplish-black insoluble precipitate appears in the tissue.[9] The nature of this deposit resulting from the incompatibility of the two dyes is unknown. Straus et al,[10] also demonstrated the reducing enzymes in neoplasms through use of the colorless tetrazolium salts, finding a differential reduction of the tetrazolium by carcinomatous tissue as compared to the rate exhibited by the surrounding tissues. When tetrazolium salts are reduced (through addition of 2 hydrogen atoms, there result insoluble red substances known as formazons. It is quite probable the tetrazolium salts may likewise be precipitated in differential quantities in some neoplastic tissues, which may be useful in the therapy of malignant processes.

tained by treating the serum, and pressed cancer tissue, with digestive enzymes to separate the proteins, the remaining fluid being centrifuged to separate the "carcinogenic viruses." (This material could be subject to analysis through an electrophoresis apparatus by the illuminated graph method.) The injection of the isolated material antigens should initiate body response with the formation of specific corresponding enzymes.

Normal serum, to a certain extent, causes degeneration and lysis of cancer cells; this ability is lacking in the serum of cancer that contains a cancer-protecting or antilytic agent. It is presumed that this lysing agent is allied to the amino acids and their specific enzymes. As lymph fluid has a low protein content, it probably does not contain a high concentration of the lytic anticarcinoma factor. Normal dried blood plasma obtained by the high vacuum-cold process appears to retain some anti-enzyme cancer-inhibiting agent of cytolytic nature and causes a systemic reaction when administered to a carcinomatous subject. Cancer serum itself has no toxic properties but when added to normal serum it acquires toxicity. It is presumed that abnormal unidentified enzymes in the cancer tissue, and serum, react with components of normal serum to produce this toxicity.

It is difficult to assess the modus operandi and value of such therapeutic modalities as radium, roentgen ray, iodoacetic acid and iodoacetate, methylnaphthaquinone, magnesium chloride, methylene blue, toluidine blue, iodonitrobenzoic acid, metadinitrobenzene, zinc chloride, phosphocreatin, lanolin, parathyroid and adrenal cortex extracts, and extracts of spleen, striated muscle and connective tissue. Some of these agents have ambivalent properties, that is, they can induce or inhibit cancer growth depending on the concentration. Several are definite protoplasmic poisons, and mitotic inhibitors, while others inhibit the growth by inducing fibrosis and connective-tissue formation in and about the growth with the walling off of the vascular and lymphatic systems. Some also aid in the restoration of proper tissue enzymosis, with restoration of the acid-base equilibrium and the proper metabolic activities of the cells. There is no experimental evidence that any of these measures will increase the calcium content of the diseased cells.

More recent data tend to show that the extrinsic carcinogenic agents are merely the trigger mechanisms in deranging the susceptible enzyme systems, and disorganizing the sensitive cell tissue components, and that the true carcinogens result from this chain reaction by reproducing themselves much in the manner as do the viruses. A weak carcinogenic agent applied to normal tissue is carcinogenic only over a long period of time, and apparently alters normal cells, reverting their growth and ordered multiplication, to non-differentiating uncontrolled embryonic forms (embryonization). Embryonic tissue is more susceptible to carcinogenic influences. It would be interesting to learn what effect carcinogens would exert if normal mature tissue (aging cells) were grafted upon younger and embryonic tissue. Other oncological studies should be on the effects of known carcinogens on heart tissue grown in vitro. Radioactive and stable iso-

topes might be used to study the intermediary metabolism and remote mutational effects. Primary carcinoma of the heart, striated muscle and spleen is a rarity.

Lewisohn[14] states that primary carcinoma of the spleen has almost never been found, and cannot be experimentally produced, even when fragments are implanted. Metastasis to the spleen from primary growths elsewhere is also rare, and diffuse neoplastic infiltration of the spleen does not occur. Further study of striated muscle, the heart, and splenic tissues are in order, and the isolation from them of natural growth-cell inhibitors is a possibility. Considerable lactic acid is found in active striated muscle and here is readily converted to glycogen, striated muscle rarely being a primary site of carcinoma. Lactic acid, per se, has no carcinogenic property but it may be concerned in the tissue breakdown, and mitotic stimulation through release of autolytic degradation products.

Suntzeff and Carruthers[8, 10] have shown that there is a 50% reduction of total calcium in methylcholanthrene-induced epidermal hyperplasia from that of normal epidermis, and in squamous cell carcinoma a still further reduction of about 60% from precancerous hyperplastic epidermis. Brunschwig et al[2, 11] also found a sharp drop of calcium in carcinomatous tissue.

Lansing[3] stated that if cessation of growth is a significant factor in aging, and if a mechanism involving calcium increase is an integral part of the system, one would expect to find the opposite situation in cancer. Cancer may be regarded as a very youthful and vigorous tissue with tremendous and uncontrolled growth capacity, and, of necessity, requires more protein for nourishment. Lansing studied the nature of the calcium decrease in hyperplastic mouse epidermis and resulting carcinomata by means of ultrafiltration. It was found that the ultrafilterable calcium fraction of a squamous cell carcinoma was sharply reduced on both an absolute and relative basis, and that the base-binding capacity of an organic fraction which binds calcium is altered in some manner in cancer. This factor, most likely, rests in the disturbed enzyme systems, and the lowered *p*H of the malignant tissue—the result of failure of conversion of the lactic acid which is neutralized by the calcium and other alkaline material present. This suggests a phenomenon which is not difficult to explain upon biochemical grounds. Excess calcium in tissue is no proof that such tissue is immune to cancer, nor that excess production of lactic acid need lead to the development of carcinoma.

Coman[5, 12] has found that normal cells are more readily separated by micro manipulation when in calcium-free medium than when in balanced salt solution, and has demonstrated that cancer cells are more readily separated than are normal cells. He believes that the decreased adhesiveness of cancer cells results from a local calcium deficiency which facilitates separation of these cells from one another.

Lansing[3] offers an alternate hypothesis that an organic calcium-binding complex of the cell cortex plays an integral part in the growth-regulatory mechanism of cells, and that at the time of cessation of growth this calcium-

binding complex, presumably a protein, is altered or reoriented in such a way as to increase calcium-binding capacity. Thus a mechanism is offered which at least in a general way synchronizes the changes that occur with age.

When the calcium-binding system becomes altered in such a manner as to decrease calcium binding, growth does not cease, age changes do not occur, and, in effect, the state of affairs exists that it is associated with cancer. This hypothesis is also compatible with Coman's concept of the invasiveness of cancer.

Conclusions

A summary of the evidence shows that long-continued alkalemia and alkalotic states predispose to atherosclerosis, Paget's disease, Buerger's disease, myositis ossificans, certain other calcium metabolic disorders, and bone and joint affections.

An alkalemia arises through an uncompensated carbon dioxide deficit resulting fron loss of HCl by vomiting, disturbances in such enzyme systems as carbonic-anhydrase, hexosephosphate, ingestion of alcohol until it reaches a high concentration in the blood, forced or shallow breathing, asphyxia, hyperventilation induced by high altitudes and hot bathing, vasoconstricting drugs, tea, coffee and tobacco, fluorine compounds, parathyroid extract, disordered parathyroid metabolism, diets limited mainly to milk and eggs, or fruit and vegetables on account of their excess base-forming elements.

A prolonged alkalemia results in a supersaturation of the blood with lipid and calcareous matter which is precipitated because of the increased *p*H. Such deposition occurs in specific tissues more reactive to changes in the acid-base equilibrium. The tiny vasa vasorum first become obstructed by lipid and lime material. This results in anemic, ischemic and anoxic states of the arterial vessels. Local anemia and anoxia favor calcification. Any tissue more alkaline in nature, whose CO_2 production is minimal, is liable to fibrosis and calcium-lipid depositions.

An alkalemic state acts as a stimulus to the vasomotor center to cause further vasoconstriction and a general rise in blood pressure; it neutralizes the organic acids necessary for maintaining the acid-base equilibria and the salts in solution.

Abnormal alkali retention is an etiologic factor in hypertension. An excess or retention of such bases as sodium bicarbonate causes a rise in the blood pressure, and prevents the release of the oxygen in hemoglobin. This leads to lowered tissue respiration and local ischemic anemic and anoxic areas in susceptible soft tissues and consequent fibrosis and tissue breakdown.

Alkali tolerance tests should reveal potential or latent hypertension, pre-atherosclerotic and like states by showing alkali retention. Long-standing alkalemia and extended alkalotherapy exert destructive effects upon other essential agents as for example the vitamins C and B-complex, minerals, etc., and lead eventually to signs of these deficiencies.

A defective blood-enzyme state (e. g., a fault in the carbonic-anhydrase enzyme) prevents proper conversion of CO_2 to carbonic acid, and results in an alkalemia and alkalosis.

In neoplastic growth there is a marked disorder in the enzyme systems, especially those that participate in the intermediate steps of glycolysis in connection with the carbohydrate and hexosephosphate metabolism. In consequence there is a deficiency of glycogen, and an excess production of acid that draws so much upon such tissue-cell elements as calcium, magnesium, sodium and other alkaline agents that a state of insufficiency arises.

Efforts should be directed toward restoration of the acid-base equilibrium of the affected tissues and the normal enzyme systems. Inducing fibrosis and connective tissue in and about the diseased areas would also act to inhibit further cancer growth and metastasis.

Cancer tissue results from a disturbance in the sensitive tissue-cell-enzyme systems produced by either intrinsic or extrinsic means. Aberrations in cellular metabolism produce nuclear degradation products, or carcinogenic viruses, which stimulate abnormal cell growth, hyperplasia, tissue breakdown with the production of toxic products. It is postulated that carcinogenic agents reverse the growth and multiplication of normal mature cells to non-differentiating tissue of uncontrolled embryonic form (embryonization) which has become irreversibly altered, both physically and chemically.

In normal plasma, and the dessicated product, there is a cancer-inhibiting agent that is not present in the plasma of cancer subjects. This agent should be investigated further for proper identification, and put to some therapeutic and diagnostic use.

The study of the physiology of the acid-base equilibrium shows the importance of metabolic disturbances in the origin and the development of certain pathological processes, though some of these depend upon special dysergic conditions of the patient. Blood and tissue examinations should include *p*H determinations, if possible. If the *p*H varies from the norm, the causes should be ascertained and corrective measure instituted. A simplified method is needed for determining the *p*H of body tissues and fluids.

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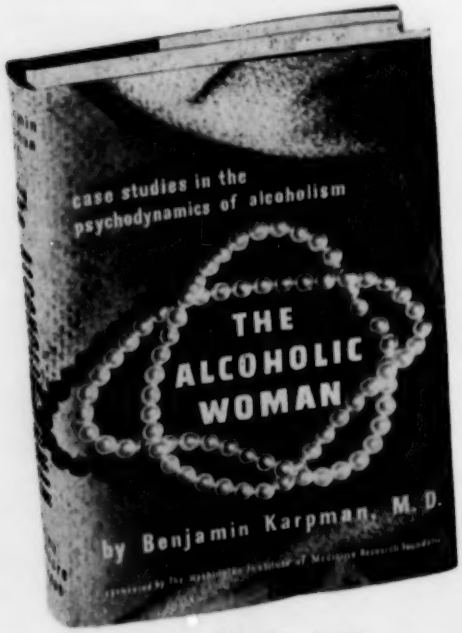

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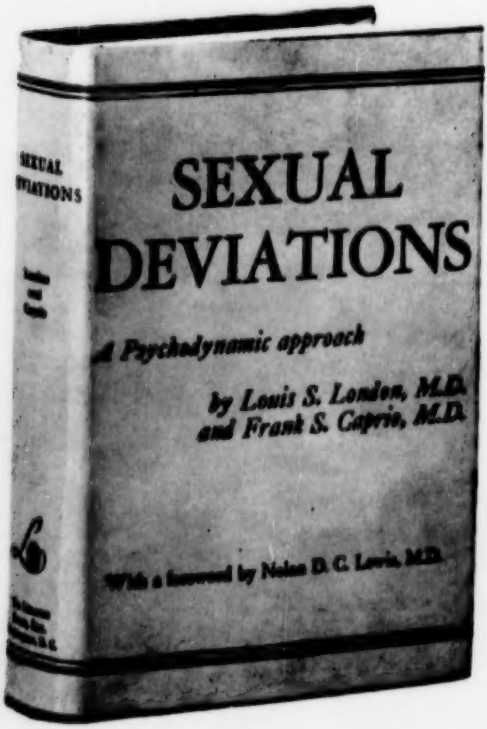
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